ATTACHMENT 2

DECEMBER 18, 1998
JUNE 2, 1999
TSEAC MEETINGS:
AGENDA
ISSUE PAPER
VOTE SUMMARY

NOTE: TRANSCRIPTS OF THE DECEMBER 1998 AND JUNE 1999 TSEAC MEETINGS ARE AVAILABLE AT:

http://.fda.gov/ohrms/dockets/ac/acmenu.htm

FOOD AND DRUG ADMINISTRATION

TRANSMISSIBLE SPONGIFORM ENCEPHALOPATHIES ADVISORY COMMITTEE

Holiday Inn
8120 Wisconsin Avenue - Bethesda, Maryland 20814
December 18, 1998

Agenda

8:00 a.m. Opening and Administrative Remarks
William Freas, Ph.D., Executive Secretary, TSEAC, FDA

8:15 a.m. Introductory Remarks
Randolph Wykoff, M.D.,
Associate Commissioner for Operations, FDA

NEW VARIANT CREUTZFELDT-JAKOB DISEASE AND BOVINE SPONGIFORM ENCEPHALOPATHY: Issues relevant to the Safety of Blood, Blood Components and Plasma Derivatives

8:25 a.m. Background
Mary Elizabeth Jacobs, Ph.D.
Office of Blood Research and Review, CBER, FDA

8:45 a.m. nvCJD: Characteristics and Demographics
Robert G. Will, M.D.
National CJD Surveillance Unit
Edinburgh, Scotland, UK

9:15 a.m. Experimental Studies of Blood Infected with TSE Agents
Robert G. Rohwer, Ph.D.
Molecular Neurovirology Laboratory
Veterans Affairs Medical Center
Baltimore, Maryland

9:45 a.m. 1. Role of Circulating Lymphocytes in Pathogenesis of TSEs
2. BSE, nvCJD and Blood: a European View
Prof. Adriano Aguzzi, M.R.C. Path.
Institute of Molecular Biology
University of Zurich, Zurich, Switzerland

10:05 a.m. **BREAK**

10:20 a.m. Current Status of the BSE Epidemic in Europe: USDA Perspective
Lisa Ferguson, D.V.M.
Senior Staff Veterinarian
Animal and Plant Health Inspection Service, Riverdale, Maryland

10:35 a.m. Committee Discussion

BLOOD DONOR DEFERRAL, PRODUCT WITHDRAWALS AND PRODUCT SHORTAGES

10:55 a.m.	US Blood Donor Deferral Policies **CAPT Mary Gustafson** **Director, Division of Blood Applications** **Office of Blood Research and Review, CBER, FDA**
11:15 a.m.	Current Regulatory Policies in the United Kingdom Regarding TSEs and Safety of Blood, Blood Components and Plasma Derivatives **Dr. Jeremy S. Metters, C.B.** **Deputy Chief Medical Officer** **Department of Health** **London, England, UK**
11:35 a.m.	Current Regulatory Policies in Canada Regarding TSEs and Safety of Blood, Blood Components and Plasma Derivatives **Douglas Kennedy, Ph.D.** **Division of Blood Borne Pathogens** **Bureau of Infectious Diseases** **Laboratory Centre for Disease Control** **Ottawa, Canada**
11:45 a.m.	Committee Discussion
12:00- 1:00	**LUNCH**
1:00 p.m.	REDS Study **Alan Williams, Ph.D.** **American Red Cross, Holland Laboratories** **Rockville, Maryland**
1:15 p.m.	Effects of Withdrawal and Recall Policies on the Supply of Plasma Derivatives in the U.S. **Mark Weinstein, Ph.D.** **Director, Division of Hematology** **Office of Blood Research and Review, CBER, FDA.**
1:30 p.m.	Open Public Hearing
2:30 p.m.	Committee Discussion and Votes
5:15 p.m.	Dura Mater Allograft: Update **Celia M. Witten, Ph.D., M.D.** **Center for Devices and Radiological Health, FDA**
5:30 p.m.	Adjourn

ISSUE SUMMARY
TRANSMISSIBLE SPONGIFORM ENCEPHALOPATHIES ADVISORY COMMITTEE
DECEMBER 18, 1998 BETHESDA, MARYLAND

ISSUE: Should FDA recommend the deferral from blood donation of persons with possible foodborne exposure to Bovine Spongiform Encephalopathy (BSE) as a precautionary measure to reduce the risk of blood transmission of new variant Creutzfeldt-Jakob Disease (nvCJD)?

BACKGROUND: Consideration of this issue follows the February, 1998, decision of the United Kingdom (UK) not to use UK-sourced plasma for manufacturing blood derivative products as a precautionary measure in order to reduce the theoretical risk of transmission of nvCJD by plasma derivatives. The decision was based upon advice from the UK Committee on Safety of Medicines and followed three recalls of blood products in November, 1997, because donors subsequently developed nvCJD. That decision did not affect transfusion use of whole blood from UK donors. In addition, in July, 1998, the UK Department of Health accepted the advice of the Spongiform Encephalopathy Advisory Committee to leucodeplete (leukoreduce) all blood for transfusion as a precautionary measure. That decision is currently being implemented in the UK.

Although no cases of nvCJD have occurred in the US, FDA's current policy is that plasma derivatives should be retrieved, quarantined, destroyed and consignees notified in the event that in-date products were found to have been manufactured from a donor who later developed nvCJD (September 8, 1998). Based upon a review of the published epidemiological studies by the Centers for Disease Control and Prevention, withdrawal of plasma derivatives made from a donor who later developed conventional CJD is not recommended. These policies were announced by Dr. David Satcher at the August 27, 1998, meeting of the Advisory Committee on Blood Safety and Availability to the Department of Health and Human Services.

The scheduled presentations will review (1) current information on nvCJD characteristics and demographics; (2) animal and laboratory studies relevant to potential transmission of the infectious agent of nvCJD through blood, blood components, or plasma derivatives; (3) status of the BSE epidemic; (4) US donor deferral policies; (5) policies in the UK, Canada, and Europe; (6) issues of supply and potential shortages. (Please note that cost related issues would be brought before the Public Health Service Advisory Committee on Blood Safety and Availability.)

DISCUSSION: Some specific concerns which can be addressed in the context of answering questions to the committee are:

- based on current scientific knowledge, is there a potential risk of transmission of nvCJD via blood or blood products?
- do the data support the hypothesis that the same agent is responsible for BSE in cattle and nvCJD in humans?

- have any processes been shown to inactivate the agent responsible for BSE? For nvCJD?

- can the potential risk of transmission of nvCJD via blood products be estimated based upon current available data?

- are there particular fractions or components of blood products which should be considered to carry a greater risk of transmission of nvCJD? Are there particular fractions or components of blood products which should be considered to carry no, or lesser, risk for transmission of nvCJD?

- when comparing nvCJD to CJD, based on human, animal, and laboratory data, can the risk of transmission by blood or blood products be considered higher, the same, or lower for nvCJD?

- are there any laboratory or other test methods which might identify blood products with the potential to transmit nvCJD? Are they currently adaptable for large-scale screening?

- can individuals at increased risk for nvCJD be identified? Is there a genetic or physical predisposition?

- Is the risk associated with foodborne exposure well characterized? Can it be quantified with factors such as amount, length of time, or type of food consumed? Is dietary history (i.e., non-vegetarian) useful to identify individuals at increased risk?

- based on scientific knowledge, should additional donor deferral criteria be considered to reduce the possible risk of nvCJD?

- what would be the estimated impact on the supply of blood and blood products in the US of additional donor deferral criteria?

Note that the committee is not being asked for a recommendation on universal leukoreduction at this time. At its September 18, 1998, meeting, the Blood Products Advisory Committee recommended universal leukoreduction of all non-leukocyte transfusion blood components. FDA plans to address cost-related impacts of leukoreduction at the DHHS Advisory Committee on Blood Safety and Availability in January, 1999.

QUESTIONS: The questions to be considered by the committee at the conclusion of these presentations and discussions follows as ' ——— '. The committee's recommendations will be used to develop FDA's policy.

BACKGROUND MATERIALS: Also enclosed are documents that may be useful for the committee members in preparing for the discussions, which include: (———) original scientific papers; ' ——— . USDA interim rule Restrictions on the Importation of Ruminants, Meat and Meat Products From Ruminants, and Certain Other Ruminent Products, and USDA evaluation criteria for BSE status of a country with accompanying questionnaire; (——— , FDA's September 8, 1998, announcement "Change to the Guidance Entitled 'Revised Precautionary Measures to Reduce the Possible Risk of Transmission of Creutzfeldt-Jakob Disease (CJD) by Blood and Blood Products'" addressing withdrawal policies for CJD and nvCJD, and FDA's December 11, 1996 Memorandum; ' ——— , Summary of the

Clinicopathological Features of Transmissible Spongiform Encephalopathies (TSEs) in Humans and Creutzfeldt-Jakob Disease and Blood Safety Data Presented to DHHS Advisory Committee on Blood Safety and Availability, January 28, 1998, with Some Updates Through June 1998, provided by Drs. Schonberger and Belay; (. ————) UK Department of Health statements on UK-sourced plasma and leucodepletion; (/ ————) AABB donor questions; (/ ———— . papers concerning the Retrovirus Epidemiology Donor Study (REDS).

DRAFT SUMMARY ANSWERS TO THE
QUESTIONS PRESENTED TO TSEAC
on December 18, 1998

1. Should FDA recommend new deferral criteria for blood donors to attempt to reduce the theoretical risk for transmitting new variant Creutzfeldt-Jakob disease (nvCJD) by excluding donors potentially exposed to the agent of bovine spongiform encephalopathy (BSE)?

The committee voted: 9 yes and 6 no votes.

Before considering part "a" of this question, the committee voted to drop the term "or other BSE Country" with a vote of 15 yes votes (unaminous) to drop the phrase.

a) Should FDA recommend excluding donors who have resided in the United Kingdom ~~or other BSE country~~?

b) Should FDA recommend distinguishing between donors who were resident in BSE countries during periods of higher vs. lower risk of exposure to the BSE agent?

c) Should FDA recommend exclusion of donors who had less intense exposure to beef products based on limited travel to a BSE country? (When did they travel, how long were they there, what did they eat?)

For parts a to c of question 1, the committee decided it would be best to make the decisions after more data is obtained. They suggested that someone should conduct a survey of those who donate blood with the following suggested three questions: 1. Have you lived in great Britain between 1980 and now? 2. If so when? 3. For how long? They took a vote (12 were in favor of taking this survey, 1 was opposed). The committee would prefer not to advise FDA on criteria for donor exclusion until more information is available.

Initially the committee did **not** want to discuss "withdrawals" parts d and e of question 1, without knowing what "criteria" would be used. They then discussed parts d and e (question 1) for "any" criteria that they would eventually accept.

d) Should FDA recommend withdrawal for blood components based on these donor deferral criteria?

The committee voted: 7 yes, 5 no votes.

e) Should FDA recommend withdrawal for plasma derivatives based on these donor deferral criteria?

The committee voted: 11 no,1 yes votes.

2. FDA plans to refer possible nvCJD cases to CDC for investigation. Considering FDA's precautionary withdrawal policy for nvCJD:

   a) Should FDA recommend precautionary quarantine or withdrawal for plasma derivatives to which a possible nvCJD donor contributed pending histological/immunohistochemical/other confirmation of the clinical diagnosis?

The committee voted: 8 yes, 1 no, 1 abstain.

   b) Is a tonsil biopsy negative for protease-resistant prion protein sufficient to make product withdrawals unnecessary or to reinstate products to which a donor with a possible diagnosis of nvCJD contributed?

The committee voted: 3 abstain, 6 no votes

The committee suggested that the responsible agency (CDC) develop and provide the FDA with clearly defined diagnostic criteria for "possible nvCJD", "probable nvCJD" and "confirmed nvCJD".

FOOD AND DRUG ADMINISTRATION

TRANSMISSIBLE SPONGIFORM ENCEPHALOPATHIES ADVISORY COMMITTEE

Holiday Inn - Gaithersburg
2 Montgomery Village Avenue, Gaithersburg, Maryland 20879
June 2-3, 1999

AGENDA

Wednesday, June 2, 1999

8:30 a.m. Opening
Paul Brown, M.D., Committee Chair

8:35 a.m. Administrative Remarks
William Freas, Ph.D., Executive Secretary, TSEAC, FDA

8:45 a.m. Introductory Remarks
Randolph Wykoff, M.D.
Associate Commissioner for Operations, FDA

Topic 1. DEFERRAL OF BLOOD DONORS BASED UPON FOODBORNE EXPOSURE TO BSE AGENT: DONOR SURVEY RESULTS, TIME COURSE OF THE BSE EPIDEMIC AND ITS RELATIONSHIP TO nvCJD, RISK ESTIMATES, AND RESERVE CAPACITY OF THE US BLOOD SUPPLY

8:55 a.m. Background
Mary Elizabeth Jacobs, Ph.D.
Office of Blood Research and Review, CBER, FDA

9:10 a.m. Results of Survey of US Blood Donors Conducted by the American Red Cross, American Association of Blood Banks, America's Blood Centers, and the National Heart, Lung, and Blood Institute
Alan Williams, Ph.D.
American Red Cross, Holland Laboratories
Rockville, Maryland

9:50 a.m. Open Committee Discussion

10:30 a.m. Break

10:45 a.m. Demographics of BSE, Associated UK Regulatory Decisions, and Time Course of nvCJD
Christl Donnelly, Sc.D.
Head, Statistics Unit
Welcome Trust Centre for the Epidemiology of Infectious Diseases
University of Oxford, UK

Wednesday, June 2, 1999 (continued)

11:15 a.m.	Det Norsk Veritas Risk Assessment **Philip Comer** **Director of Client Services** **Det Norsk Veritas, UK**
11:50 a.m.	Reserve Capacity of the US Blood Supply: Summary of the April 29-30, 1999, Meeting of the Advisory Committee on Blood Safety and Availability **Stephen D. Nightingale, M.D., Executive Secretary** **Advisory Committee on Blood Safety and Availability**
12:30 p.m.	Canadian National Blood Safety Council Open Forum **Penny Chan, Ph.D., MHSc.** **Scientific Secretariat** **National Blood Safety Council** **Canada**
12:45 p.m.	Lunch
1:45 p.m.	Open Public Hearing
2:45 p.m.	Committee Discussion and Vote
4:15 p.m.	Operational Definition of possible nvCJD Case for Quarantine of Blood and Blood Products **Dorothy Scott, M.D.** **Division of Hematology** **Office of Blood Research and Review, FDA**
4:35 p.m.	Committee Discussion
5:30 p.m.	Break for the day

FOOD AND DRUG ADMINISTRATION

TRANSMISSIBLE SPONGIFORM ENCEPHALOPATHIES ADVISORY COMMITTEE

Agenda (continued)

SECOND DAY, Thursday, June 3, 1999

8:30 a.m. Reconvene

Topic 2. Proposed Revisions to Guide for 510(k) Review of Processed Human Dura Mater
Charles Durfor, Ph.D.,
Center for Devices and Radiological Health, FDA

Topic 3. Safe sourcing of sheep-derived and goat-derived materials contained in or used to manufacture FDA-regulated products

9:00 a.m. Background and introduction of issue regarding materials derived from sheep and goats in FDA-regulated products
David Asher, MD.
Center for Biologics Evaluation and Research, FDA

9:50 a.m. Potential risk of introducing BSE agent into sheep and goats in Europe
Professor J. Almond, Ph.D.
Pasteur-Merieux Connaught, France

10:10 a.m. Break

10:25 a.m. Scrapie in sheep and goats: Tissue infectivity
Richard Race, D.V.M.
NIAID, NIH (by teleconference)

10:35 a.m. Questions for Previous Speakers

10:50 a.m. Potential for human and animal exposures to animal TSE agents in the USA
Diane Sutton, D.V.M.
Animal and Plant Health Inspection Service, USDA, Riverdale, Maryland

11:20 a.m. FDA regulation for ruminant feed
John Honstead, D.V.M.
Center for Veterinary Medicine, FDA

Agenda (continued)

Thursday, June 3, 1999

11:30 a.m.	Measures for consideration in assuring scrapie-free sources of sheep-derived and goat-derived materials from countries with scrapie **Lisa Ferguson, D.V.M.** **Animal and Plant Health Inspection Service, USDA, Riverdale, Maryland**
11: 50 a.m.	Questions for previous speakers
12:00	Lunch
1:00 p.m.	Open public hearing
1:30 p.m.	Committee charge and presentation of questions **Kiki B. Hellman, Ph.D.** **Center for Devices and Radiological Health, FDA**
1:35 p.m.	Committee Discussion and Votes
4:30 p.m.	Adjourn

ISSUE SUMMARY
TRANSMISSIBLE SPONGIFORM ENCEPHALOPATHIES ADVISORY COMMITTEE
JUNE 2, 1999 GAITHERSBURG, MARYLAND

ISSUE: On December 18, 1999, the Committee voted to recommend deferral of blood donors with possible foodborne exposure to BSE in the United Kingdom (UK) as a precautionary measure to reduce the theoretical risk of new variant CJD (nvCJD). At the committee's recommendation, a survey of blood donors for travel/residence in the UK has been conducted. What time period of travel/residence and time period of the BSE epidemic should FDA recommend for donor deferral? Should the deferral criteria apply both to whole blood donations and to plasma for fractionation?

BACKGROUND: Consideration of this issue follows the December 18, 1999 TSEAC meeting. The Issue Paper, questions to the committee, agenda, and summary of committee votes are included in the background material. The complete transcript of the meeting is at www.fda.gov/ohrms/dockets/ac/cber98t.htm.

The scheduled presentations will review (1) the results of the survey; (2) the time course of the BSE epidemic; (3) modeling the risk to humans of transmission by blood; (4) the reserve capacity of the US blood supply; and (5) a brief review of parallel discussions in Canada.

DISCUSSION: Some specific concerns, which can be addressed in the context of answering questions to the committee, are:

Decisional Issues

- Based on survey results and scientific knowledge, will additional donor deferral criteria reduce the possible risk of nvCJD?
- What would be the estimated impact on the supply of blood and blood products in the US of additional donor deferral criteria?
- Should the donor deferral criteria be the same for whole blood and for source plasma?

Related Issues:

- Can the time course of the BSE epidemic be described?
- Is the impact of the feeding ban and other restrictions known?
- Can the time course of the BSE epidemic be related to the risk of foodborne exposure to the BSE agent? Is the risk of foodborne exposure well characterized? Can it be quantified with factors such as amount, length of time, or type of food consumed? Is dietary history (e.g, eating meat) useful to identify individuals at increased risk?
- Can the risk of developing nvCJD be related to the time course of the BSE epidemic?

- Can individuals at increased risk for nvCJD be identified? Is there a genetic or physical predisposition?
- Can the potential risk of transmission of nvCJD via blood products be estimated based upon current available data?

QUESTIONS: The questions to be considered by the committee at the conclusion of these presentations and discussions follows as
The committee's recommendations will be used to develop FDA's policy.

BACKGROUND MATERIALS: Also enclosed are documents that may be useful for the committee members in preparing for the discussions, which include: (——— Agenda, Issue Paper, and summary of votes from December 18, 1999 TSE Advisory Committee meeting; (——— , scientific papers relevant to nvCJD in addition to those distributed for the December, 1998, meeting; (———) information and scientific papers relevant to BSE and related papers on nvCJD; (Det Norsk Veritas risk assessment; (———) nvCJD papers by Dr. Robert Will distributed for the December, 1998, meeting; (———) letter received from the Department of Defense; and (——— , Summary of Meeting of the Advisory Committee on Blood Safety and Availability, April 29 and 30, 1999 addressing the reserve capacity of the US blood supply.

TSEAC
June 2 & 3, 1999

"Quick Summary"

TOPIC 1

The committee modified the original questions slightly. They then voted on the following questions:

1a. Should FDA recommend new deferral criteria for donors of transfusible components to reduce the theoretical risk of transmitting nvCJD from transfusions based on donor exposure to BSE in the UK?

Vote: 12 yes, 9 no votes, 0 abstained

1b. If so, what deferral criteria should FDA recommend (i.e. time period, nature and length of exposure)?

The committee did not try to reach a consensus on this topic but wanted to provide the raw data following a poll of committee members. The length of exposure results were as follows:

Three members wanted it to be five years or over
One member wanted it to be three years or over
Five members wanted it to be one year or over
Seven members wanted it to be six months or over
Four members wanted it to be four months or over
One member abstained from voting

2a. Should FDA recommend new deferral criteria for donors of source plasma and recovered plasma for further manufacture into injectable products to reduce the theoretical risk of transmitting nvCJD from plasma derivatives based on foodborne exposure to BSE in the UK?

Vote: 12 yes, 8 no votes, 0 abstained

2b. If so, what deferral criteria should FDA recommend (i.e. time period, nature and length of exposure)? The committee did not vote on this question as written, but voted on keeping the criteria for question 1 b the same as criteria for question 2b.

Vote: 19 yes, 0 no votes, 0 abstained

The committee heard a presentation proposing an operational definition of possible nvCJD Cases for quarantine of blood products. Committee member's comments were that the proposal was a good "template" to follow. Some members would prefer not to use the label "possible nvCJD". They felt that FDA should keep its criteria flexible and compatible with those of CDC and the UK.

TOPIC 2

The committee received a presentation on the historical background and current status for the document, "Guidance for the Preparation of a Premarket Notification Application for Processed Human Dura Mater". Members of the committee discussed the proposed guidance and suggested further discussions on the topic of dura mater, either at committee meetings or workshops.

TOPIC 3

The committee received presentations on: the potential risks to humans from TSE agents of animal origin (such as BSE and scrapie), the presence of sheep-derived and goat-derived materials in FDA regulated implantable and injectable products; and current FDA procedures, governmental regulations, policies and practices, that are in place to protect humans from exposure to TSEs. The committee discussed these risks and possible precautions to reduce these risks. The committee recommended that the risks be minimized. They made several suggestions such as increasing monitoring of sheep flocks and promoting "scrapie-free flocks". They encouraged current scrapie-free certification programs in the United States, as well as similar efforts in other countries. They suggested that we not rely solely on imports from scrapie-free countries.

The committee members with FDA staff modified the original discussion questions and voted on the following version of questions:

1. Should the FDA take measures to ensure that sheep and goats originating from or residing in countries where BSE occurs are safe sources of materials for manufacture of FDA-regulated products intended for injection or implantation (both as components of the products and as manufacturing-process reagents?

Vote: 14 Yes, 0 no, 0 abstained

2. Should the FDA take measures to ensure that sheep and goats originating from or residing in countries where scrapie occurs are scrapie-free and acceptable sources of materials for manufacture of FDA-regulated products intended for injection or implantation, both as components of products and manufacturing-process reagents.

Vote: 13 Yes, 1 no, 0 abstained.